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Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression

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Abstract

The aim of this treatment study was to evaluate the therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) over the right parietal cortex in depression. In a double-blind, sham-controlled design ten consecutive sessions of 2 Hz rTMS (inter-pulse interval 0.5 s) at 90% motor threshold to the right parietal cortex (2400 pulses per session) were applied to 34 patients with the primary diagnosis of DSM-IV depression and a score of ≥ 15 on the 17-item Hamilton Rating Scale for Depression (HAMD). The primary outcome measures were the percentage change from baseline on the 17-item HAMD scores after ten sessions, and the percentage of clinical (defined as $\geq 50\%$ reduction in HAMD score) and partial clinical (defined as $\geq 30\%$ reduction in HAMD score) responders. Reduction of HAMD scores in the real rTMS treatment (mean_{real} \pm S.D., $-19.9 \pm 32.5\%$) was not statistically different from the sham rTMS treatment (mean_{sham} \pm S.D., $-5.6 \pm 28.4\%$), and the number of clinical responders did not differ between treatments. However, a significant greater number of partial clinical responders were observed in the real (43.8%) compared to the sham rTMS treatment (6.3%). This study provides the first evidence showing that 2 Hz rTMS over the right parietal cortex may have antidepressant properties, and warrants further research.

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Introduction

Ever since the first positive effects on mood were observed in two depressed patients after undergoing repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex (PFC), rTMS has been explored as a safe and non-invasive method to treat clinical depression (Hoflich et al., 1993). Earlier findings showing tonic reductions in left anterior activity in depression (Baxter et al., 1989) inspired researchers to apply fast frequency (≥ 10 Hz) rTMS to increase left PFC activity (e.g. Avery et al., 2006; George et al., 1997; Koerselman et al., 2004). A recent meta-analysis

examining 30 double-blind, sham controlled rTMS treatment studies performed over the past 20 yr, showed that fast-frequency repetitive rTMS over the left PFC is superior to sham rTMS but is only moderately effective in treating non-psychotic depression (Schutter, 2008). Although the antidepressant efficacy of rTMS is comparable to several commercially available pharmacological agents (Kirsch et al., 2008), several suggestions have been made to further improve the effectiveness of rTMS. These include, among others, prolongation of treatment duration, intensification of stimulation parameters, and consideration of brain regions other than the PFC (Herrmann and Ebmeier, 2006; Loo and Mitchell, 2005; Schutter and van Honk, 2005). Indeed, different treatment durations and stimulation parameters have been investigated (e.g. Fitzgerald et al., 2003; O'Reardon et al., 2007). Despite the fact that meta-analytical studies show that rTMS applied to DLPFC has antidepressant properties, they

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remain inconclusive concerning clinical efficacy. Several methodological strategies have been proposed to improve the efficacy of DLPFC rTMS which among others includes using higher stimulation intensities, prolonged treatment duration and increased stimulus frequency (Loo and Mitchell, 2005). However, structural, functional and chemical abnormalities associated with depression are not limited to the DLPFC exclusively (Ressler and Mayberg, 2007). The exploration of the antidepressant effects of rTMS to brain regions other than the DLPFC may therefore also be worthwhile (Schutter and van Honk, 2005). The stimulation of alternative brain regions may identify other cortical areas importantly involved in the pathophysiology of depression and might perhaps contribute knowledge to future rTMS treatment studies. To the best of our knowledge, no clinical studies have as yet addressed other cortical brain regions for rTMS in the treatment of depression.

Lesion and neuroimaging studies in humans suggest that the parietal cortex could be a candidate alternative cortical region (e.g. Heller and Nitschke, 1998; Mayberg et al., 1999; Starkstein et al., 1989; Uytendhoeft et al., 1983). One line of evidence suggests that reduced activity, in particular of the right posterior parietal cortex, reflects reduced autonomic arousal and responsiveness in depression (Heller, 1993; Henriques and Davidson, 1997). In contrast, increased right parietal cortex activity has also been observed in depressed patients. It has been proposed that the role of the parietal cortex in depression is mediated by anxiety (Keller et al., 2000); a mental state characterized by increased autonomic arousal and heightened levels of attention wherein the parietal cortex is importantly involved (Heller, 1993).

Moreover, right posterior lesions have been shown to augment exploratory and approach-related behaviour in rats, whereas increased right-to-left parietal resting-state activity positively correlates to more approach-related attentional processing in non-depressed volunteers (Crowne et al., 1987; Schutter et al., 2001). Recently, in a single-blind counter-balanced rTMS experiment we explored the relationship between the right parietal cortex and emotional processing in healthy volunteers. Effects on mood, autonomic activity and motivated attention were investigated by comparing a single session of 20 min real rTMS [2 Hz, 90% motor threshold (MT), 2400 pulses] over the right parietal cortex to a single session of 20 min sham rTMS (2 Hz, 90% MT, 2400 pulses, coil tilted 90°). Results showed significant reductions in depressive mood in the real compared to sham rTMS, immediately following stimulation as well as after 30

Table 1. Demographic and clinical characteristics

| rTMS treatment characteristics | Real (<i>n</i> = 17) | Sham (<i>n</i> = 17) | <i>p</i> value ^a |
|---------------------------------|-----------------------|-----------------------|-----------------------------|
| Age, mean \pm S.D. (yr) | 44.4 \pm 11.8 | 43.8 \pm 12.5 | 0.88 |
| Female/male (<i>n</i>) | 10/7 | 7/10 | 0.49 |
| Medication (<i>n</i>) | 9 | 8 | 0.99 |
| History of ECT (<i>n</i>) | 3 | 1 | 0.60 |
| Baseline HAMD (mean \pm S.D.) | 20.9 \pm 5.0 | 21.4 \pm 6.1 | 0.83 |
| Baseline HAMA (mean \pm S.D.) | 23.5 \pm 7.4 | 24.2 \pm 7.1 | 0.78 |
| Total dropouts | 1 | 1 | 1.00 |

ECT, Electroconvulsive therapy; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

^a Two-tailed.

min. Mood changes were accompanied by autonomic-mediated and emotional responses to angry facial expressions, indicative of enhanced approach-related motivation (van Honk et al., 2003). These data in healthy volunteers provide the first evidence for a modulatory effect of rTMS to the right parietal cortex in the regulation of phenomenological, physiological and attentional aspects of depressive functioning. In sum, these findings prompted us to conduct a double-blind, sham-controlled study to evaluate the possible antidepressant effects of ten consecutive sessions of right parietal cortex rTMS with similar parameters as the study above in a sample of patients with the primary diagnosis of DSM-IV depression.

Method

Patients

Thirty-four in-patients and outpatients with the primary diagnosis of depressive disorder according to DSM-IV-TR criteria (APA, 2000) and a score of ≥ 15 on the Hamilton Rating Scale for Depression (HAMD) were enrolled in the intention-to-treat study between July 2004 and December 2007. Current depressive disorder was confirmed by the Structured Clinical Interview for DSM-IV, Research Version (SCID-I; First et al., 1996). Demographic and clinical characteristics of the patients are given in Table 1.

Exclusion criteria were history of seizures, neurological conditions, metal objects in or around the body that cannot be removed (i.e. cochlear implant, surgical clips, piercing, cardiac pacemaker), heart disease, pregnancy, drug and alcohol abuse. Patients taking psychotropic medication were accepted on the

Table 2. Psychotropic medication during real and sham rTMS treatment

| | MAOI | SSRI | SNRI | NaSSA | Neuroleptics | Hypnotics |
|-------|------|------|------|-------|--------------|-----------|
| Real | 1 | 4 | 2 | 2 | 3 | 3 |
| Sham | 0 | 3 | 4 | 0 | 2 | 3 |
| Total | 1 | 7 | 6 | 2 | 5 | 6 |

MAOI, Monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; NaSSA, noradrenergic and selective serotonergic antidepressant; Hypnotics, classical antipsychotics.

condition that antidepressant dosage had been stable for the last 6 wk and that the dosage of hypnotics had remained unchanged in the past 2 wk. Dosage and type of medication were kept constant during the treatment phase. A complete overview of medication use is shown in Table 2.

All patients received full written and verbal information on the study protocol. Written informed consent was obtained prior to enrolment. The study was approved by the medical ethical committee of Free University Medical Center and St Lucas Andreas Hospital, Amsterdam, and in accordance with the Declaration of Helsinki.

Study design

In the current double-blind, sham controlled parallel-group study patients were randomly allocated to receive either real or sham rTMS treatment on ten consecutive working days (i.e. 2 wk) via sealed envelopes opened immediately before the start of the first treatment by the clinician administering rTMS. Prior to entering the study the patient underwent standard clinical, psychiatric and laboratory tests and was screened for contraindications to rTMS. Baseline depression and anxiety scores were acquired with the 17-item HAMD and the 14-item Hamilton Anxiety Rating scale (HAMA) to assess the influence of anxiety on HAMD outcome. Clinical assessment was repeated after the final treatment session. All ratings and tests were performed by trained researchers blind to treatment. Finally, upon completion of the trial and after the final ratings patients were debriefed and asked to indicate whether they had received sham or real rTMS. At the end of the entire study patients were informed of their actual treatment. Sham rTMS-treated patients who were still classified as depressed after treatment were offered the opportunity to undergo 2 wk of real rTMS.

TMS procedure

Transcranial magnetic stimulation was performed using a high-frequency Magpro Dantec magnetic stimulator with a MCF-B65 figure-of-eight coil (Medtronic, Skovlunde, Denmark). At the start of the first session individual MT of the right hemisphere was established using the visual twitch method to determine the fixed stimulation intensity (Pridmore et al., 1998); mean \pm s.d. MT_{real} [88.3 ± 18.0 dI/dt (A/s)] and mean \pm s.d. MT_{sham} [76.9 ± 17.5 dI/dt (A/s)]. In the course of 2 wk patients received ten 20-min sessions of 2 Hz rTMS at 90% MT (i.e. 2400 pulses per session). Stimulation occurred over the P4 electrode site according to the International 10–20 EEG System targeting the right parietal cortex (Okamoto et al., 2004). The coil was held tangentially to the scalp with the handle pointing to the back and oriented away from the coil's midline at 45°. For sham stimulation a specially designed figure-of-eight coil was used. This coil mimics the sensation and sound click of real rTMS, but prevents the magnetic field from reaching the target tissue through interception by a built-in permalloy shield plate (MC-P-B70, Medtronic). Stimulation parameters and procedure were in accordance with the safety guidelines as formulated by the International Federation of Clinical Neurophysiology (<http://www.ifcn.info>). Contact between the physician applying rTMS and patient was kept to a minimum.

Statistical analyses

For the primary outcome measure a general linear model (GLM) for univariate analyses with rTMS treatment (real vs. sham) as fixed factor and the percentage change from baseline on the HAMD scores as dependent variable was performed. Baseline HAMA score, age, medication (yes/no), sex (male/female) were entered separately as covariates. Fisher's exact probability tests were used to compare the number of clinical (defined as $\geq 50\%$ reduction in HAMD score) and partial clinical (defined as $\geq 30\%$ reduction in HAMD score) responses between real and sham rTMS treatments (Mosimann et al., 2004). The success of study blinding was tested with binomial and Fisher's exact probability tests. For all tests a significance level of 0.05 (two-tailed) was applied.

Results

Tolerability of rTMS

Thirty-four patients originally entered the study. Two patients dropped out in the first week of treatment.

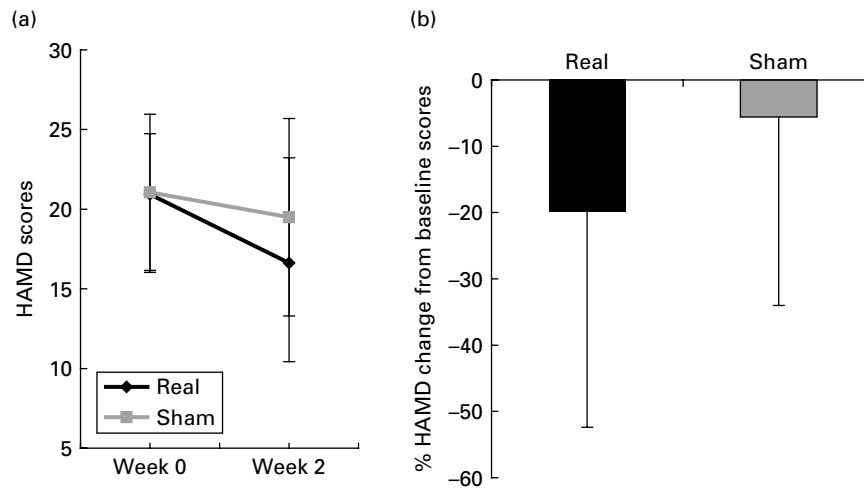


Figure 1. (a) Mean \pm s.d. Hamilton Rating Scale for Depression (HAMD) scores over time, (b) mean \pm s.d. percentage change from baseline HAMD scores after real and sham rTMS treatments.

One female medication-free patient (aged 50 yr) originally allocated in the real rTMS treatment condition withdrew from the study due to site pain. The second dropout was a male olanzapine (10 mg) and promethazine (100 mg) medicated patient (aged 49 yr) originally randomized to the sham rTMS treatment condition who experienced intolerable discomfort. In the remaining 32 patients rTMS was well tolerated and no seizures occurred. The most common reported side-effects were headache and stimulation of the right facial muscles during the first sessions.

Blinding of the study

The percentage correct guesses within the real (5/16) and sham (9/16) rTMS treatment groups did not differ from chance (test proportion 0.5) as shown by two separate binominal tests (both p values >0.4). Moreover, the real and sham rTMS treatment groups did not differ in their number of correct guesses ($p < 0.29$). These findings demonstrate that blinding of the study was successful.

Primary outcome measure

The percentage change from baseline on the HAMD scores in the real rTMS treatment (mean_{real} \pm s.d., -19.9 ± 32.8) was not statistically significant from the sham rTMS treatment [mean_{sham} \pm s.d., -5.6 ± 28.4 ; $F(1, 31) = 1.75$, $p = 0.20$, $\eta^2 = 0.06$]. Baseline HAMA scores, age, medication and sex did not influence the lack of a treatment difference (all p values >0.18). In Figure 1 the mean \pm s.e.m. HAMD decreases for real and sham rTMS treatments over time are depicted.

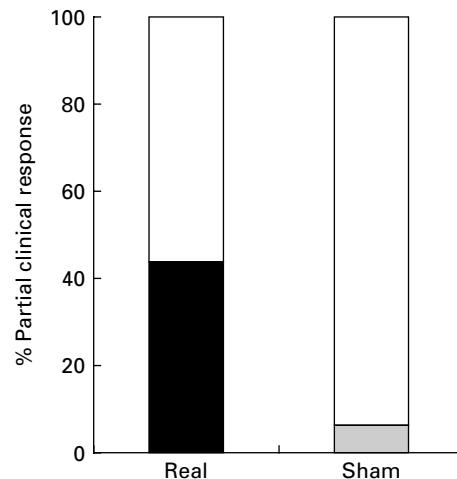


Figure 2. Significant larger partial clinical response after real compared to sham rTMS treatments to the right parietal cortex.

Fisher's exact probability test did not show a difference between number of clinical responders (defined as $\geq 50\%$ reduction in HAMD score) in the real (3/16) and sham (1/16) rTMS treatments ($p = 0.60$). However, a significant greater number of partial clinical responders (defined as $\geq 30\%$ reduction in HAMD score) was observed in the real (7/16) compared to sham (1/16) rTMS treatments ($p = 0.04$). Figure 2 shows the percentage of partial clinical responses in the real (43.8%) and sham (6.3%) rTMS treatment groups. The partial clinical responders did not significantly differ from non-responders on baseline HAMA scores, age, and MT (all p values >0.43).

Fisher's exact probability tests did not demonstrate significant medication or sex differences between partial-clinical and non-responders (both p values >0.21).

Discussion

To our knowledge, rTMS treatment studies of depression until now have targeted the PFC exclusively. This is the first treatment study that has evaluated the antidepressant effects of rTMS to the right parietal cortex in a double-blind, sham-controlled design. Despite the absence of a statistical group difference of treatment, ten sessions of real rTMS resulted in a significant larger number of partial clinical responders than sham rTMS treatment. It has been suggested that such a difference could, at least partially, be explained by individual differences in therapeutic onset in response to the intervention, a phenomenon commonly observed with antidepressant drug agents (Reid and Stewart, 2001). Regardless of these individual differences in onset we found significantly more partial clinical responders in the real compared to the sham rTMS treatment conditions providing the first evidence in support of possible antidepressant properties of rTMS over the right parietal cortex.

Baseline HAMA scores did not play a role in mediating the antidepressant effects in the treatment comparison. Neither did the partial clinical responders differ from non-responders on the HAMA score at baseline ($p=0.43$). Even though baseline HAMD scores positively correlated with HAMA score [$r(34)=0.42, p=0.013$], there was insufficient differentiation of baseline HAMA scores to evaluate whether right parietal cortex rTMS in depression is more effective in patients with comorbid anxiety (cf. Schutter and van Honk, 2005).

Furthermore, even though we failed to identify significant differences between partial clinical and non-responders on age, medication and sex, the observation that five out of the six partial clinical responders in the real rTMS treatment conditions were female is notable and concurs with recent findings showing superior antidepressant response rates in females compared to males (Yang et al., 2007; but see Conca et al., 2000). It has been suggested that steroid hormone fluctuations during the menstrual cycle may be involved (Martényi et al., 2001). Abnormal cortical excitability during the luteal phase has been found in women with premenstrual syndrome. This phenomenon has been interpreted as a result of decreased GABAergic inhibition to progesterone secretion, as evidenced by rTMS (Smith et al., 2003).

Concerning the biological basis for antidepressant effects of rTMS on the right parietal cortex, there is evidence available indicating that depression can be associated with a dysfunction of a cortico-cortical circuit, that comprises the left PFC and the right parietal cortex (Schutter et al., 2002, 2005; Schutter and van Honk, 2005). Restoration of the functional connectivity or balance in brain circuits may underlie the antidepressant properties of rTMS (Mayberg et al., 1999). Interestingly, basic neuroscientific research has shown increased functional connectivity between the left prefrontal and right parietal cortex following fast-frequency rTMS over the left PFC (Jing and Takigawa, 2000). This series of studies coincides with research on the relation between hypothalamus–pituitary–adrenal (HPA) axis dysfunction and depression, and with observations of functional cortico-cortical connectivity breakdown in depression (Belanoff et al., 2002; Cook et al., 2000; Gold et al., 2002). Additional support comes from vagus nerve stimulation in the treatment of depression. As measured with positron emission tomography during electrical stimulation of cranial nerve X in four patients with treatment-resistant major depression, Conway and colleagues (2006) found blood flow to increase in the frontal cortex and to decrease in the right parietal cortex.

Considering the fact that only 2 wk of stimulation were used the results appear promising and suggest that stimulating the right parietal cortex especially using longer treatment durations may also be therapeutically helpful in depression. Furthermore, as already noted in the Introduction, depressive disorders are more likely to be associated with dysfunctional neural networks rather than abnormalities in a single brain region. The dense connectivity between parietal and frontal cortex provides anatomical evidence for this view. It is suggested that modulating cortico-cortical networks by, for instance, simultaneously applying high-frequency rTMS to the left DLPFC and low-frequency rTMS to the right parietal cortex may yield synergetic effects. Moreover, in the modulation of cortico-cortical networks transcranial direct current stimulation (tDCS) might prove to be a valuable tool in the success of non-invasive brain stimulation in the treatment of depression (Boggio et al., 2008). In tDCS a pair of electrodes is affixed to the head in an anodal-cathodal montage through which a weak electrical current is passed. Previous research has shown that cortical excitability is increased under the anodal electrode, whereas cortical excitability is decreased under the cathodal electrode (Nitsche et al., 2007). Analogues to bilateral rTMS (Fitzgerald et al., 2006), anodal tDCS to the left DLPFC and cathodal tDCS to

the right parietal cortex could in theory be an effective way to treat depression. Alternatively, it is feasible that stimulation over any cortical region can trigger therapeutic neurobiological responses. This would mean that rTMS applied to the cortex activates the aforementioned cortico-cortical networks or subserves a 'gateway' function by activating subcortical motivational brain circuits (Strafella et al., 2001). However, recent findings from a tDCS study argues against this 'cortical generalizability' hypothesis by showing antidepressant effects in response to DLPFC tDCS, but not following tDCS to the occipital cortex (Boggio et al., 2008). These results seem to suggest that the cortical effects of rTMS are confined to association areas and depend on connections with subcortical brain regions.

Despite the fact that 43.8% of the patients showed a partial clinical response after real rTMS treatment vs. 6.3% after sham rTMS treatment, the study was hampered by several limiting factors. The fact that the percentage change in HAMD scores was not significantly different between real and sham rTMS treatments after ten sessions in 2 wk may indicate that the sample size as well as the amount of sessions were insufficient. Several recent large rTMS trials in which it was shown that real vs. sham rTMS-related antidepressant effects start to differ after 2 wk of treatment in favour of real rTMS (Avery et al., 2006; O'Reardon et al., 2007). These findings coincide with therapeutic onset delays frequently found in regular pharmacological treatments (Anderson et al., 2000; but see Mitchell, 2006). Moreover, as with the present study, many studies are hampered by improvement in depression symptoms independent of treatment condition in the first 2 wk of treatment. Possible reasons for these improvements include regaining daily life routines and increased social interactions. Longer treatment durations may therefore be necessary to dissociate general improvements from true rTMS-related antidepressant effects. In sum, we anticipate greater antidepressant effects to treatment durations of ≥ 3 wk in future studies targeting the right parietal cortex.

Although we found reductions in depressive mood after 2 Hz rTMS to the right parietal cortex in our previous study (van Honk et al., 2003), the intensity of the stimulation used in the present study may also have been too low for clear-cut effects. Indeed, there is some evidence suggesting that antidepressant responses positively vary as a function of intensity, at least with prefrontal cortex rTMS (Herrmann and Ebmeier, 2006; Padberg et al., 2002). Results from a meta-analysis on factors that modify the antidepressant effects of rTMS demonstrated that the

therapeutic effects, even though remaining significantly larger than sham rTMS, fell in studies using stimulation intensities below 90% MT, (Herrmann and Ebmeier, 2006). In contrast, no significant differences in therapeutic efficacy were observed between studies that used stimulation intensities of $< 100\%$ MT ($n = 14$) compared to studies that used stimulation intensities of $> 100\%$ MT ($n = 16$, $p = 0.65$) (Schutter, 2008). It remains debatable whether higher intensity rTMS is more effective, but the fact that scalp-parietal cortex distance appears larger than scalp-PFC distance (Knecht et al., 2005) nonetheless suggests that future studies targeting the parietal cortex in the treatment of depression might benefit from higher stimulation intensities. Furthermore, Avery and colleagues (2006) proposed that the use of flexible rather than fixed-dose designs may yield greater response rates by increasing the amount of magnetic pulses at higher intensities and sessions during treatment. Furthermore, antidepressant efficacy may be further improved by exclusively selecting a subgroup of depressed patients with comorbid anxiety for right parietal cortex rTMS treatment. Finally, the sex difference in partial clinical response is notable and suggests that hormonal fluctuations might be a potential biomarker for the efficacy of rTMS treatment.

In conclusion, in spite of the above noted limitations this study provides the first direct evidence for beneficial effects of rTMS treatment over the right parietal cortex in the treatment of depression and warrants further research.

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Statement of Interest

None.

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